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BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/779,543	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-13,21 and 30-33* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9,11-13,21 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 7-9, 11-13, and 21, and SEQ ID NO: 23702 in the reply filed on February 2, 2007 is acknowledged. The traversal is on the ground(s) that search and examination of all of the groups would not be burdensome. These arguments are moot with respect to Groups I, IV, and V, because all of the claims in these groups were cancelled in the response. Regarding Group III, Applicant's arguments regarding search burden were fully considered but were not found persuasive. MPEP 808.02 states that a serious burden results when the inventions have separate classifications, a separate status in the art, and/or a different field of search. As discussed previously, the methods of Groups II and III are materially different methods directed to nucleic acid-based detection and protein-based detection, respectively, and as such have separate classifications. Also, the methods of Groups II and III require different fields of search. A search for the elected nucleic acid detection methods of Group II would not require additional search terms directed to the protein-based detection methods of Group III. Rather, a search of the method of Group III would require additional searching in areas of the prior art unrelated to the methods of Group II. Therefore, since the methods of Groups II and III have a separate classification and require different search strategies, their examination together would impose a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

Claim 10 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 2, 2007.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos: 10/076,555, 09/217,471, 60/068,755, 60/080,664, 60/105,234, 09/297,648, 60/072,910, 60/075,954, 60/080,114, 60/080,515, 60/105,877, 60/080,666, 09/313,292, 60/085,426, 60/085,537, 60/085,696, 09/854,124, 09/400,947, 60/101,900, 09/404,706, 60/102,180, 60/102,161, 60/102,380,

60/103,815, 60/105,877, 10/629,771, 09/611,527, 60/142, 311, 60/142,310, 09/803,719, 60/188,609, 10/609,021, 09/819,150, 60/192,853, 10/615,618, 09/932,076, 60/226,326, 10/012,697, 60/254,648, and 60/275,688, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The sequence disclosures of parent Application Nos: 10/076,555, 09/297,648, 09/313,292, 09/854,124, 09/404,706, 10/629,771, 09/803,719, 10/609,021, 10/615,618, 10/012,697, and 60/532,830 are described in Table 161 on pages 63-64 of the instant application's specification. According to this table, only Provisional Application 60/532,830 discloses the instant SEQ ID NO: 23702, and as a result, none of the other prior-filed applications provide adequate support for the method of the instant claims. Thus, the effective filing date of the instant application is the filing date of Provisional Application 60/532,830 (December 23, 2003). This filing date has been used for prior art purposes.

Specification

3. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The embedded hyperlinks appear at paragraphs 279, 312, 360, 401, 459, 469, 473, 509, 595, 603, 720, 769, and 776 of the published application.

Requirement for Information

4. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

(1) What is the name of the gene product comprising SEQ ID NO: 23702 as used in publicly available databases (e.g. p53, pten, ras, vegfr)?

(2) What probes on an Affymetrix array (e.g. the HG-U133 array) hybridize to SEQ ID NO: 23702?

The information is required to identify products and services embodying the disclosed subject matter and identify the properties of similar products and services found in the prior art.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

Claim Rejections - 35 USC § 112, 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9, 11-13, 21, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of the Invention

The instant claims are drawn to methods of detecting cancerous cells, assessing tumor burden in a subject, and diagnosing cancer in a subject based on the expression level of a specific gene product (SEQ ID NO: 23702). The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The Breadth of the Claims

The instant claims 7-9 and 11-13 are broadly drawn to methods of detecting any type of cancerous cell from any organism based solely on the observation of an increase in the expression level of SEQ ID NO: 23702. Claim 7 encompasses detection of any type of cancer cell based solely on an increase in the expression level of SEQ ID NO: 23702. Claim 21 is broadly drawn to a method of assessing the tumor burden resulting from any type of cancer in any subject based solely on an observed increase in the expression level of SEQ ID NO: 23702. Claims 30-33 are broadly drawn to methods of diagnosing any type of cancer in any subject based solely on an increase in the expression level of SEQ ID NO: 23702. Claims 8 and 33 limit the cancer and cancerous cell to three types: breast cancer, prostate cancer, and colon cancer. Types of cancer and cancerous cells encompassed by the method of claims 7, 21, and 30 include breast cancer, prostate cancer, colon cancer, lung cancer, bone cancer, liver cancer, pancreatic cancer, stomach cancer, skin cancer, etc. Cancers originating or metastasizing to these different tissues inherently possess radically different etiologies and often have little relationship to one another. The methods of claims 7-9, 11-13, 21, and also encompass detection of a cancer cell from any organism (e.g. humans, monkeys, dogs, cats, rabbits, mice, rats, etc).

Guidance in the Specification and Working Examples

The specification teaches that observation of an increase in the expression level of the claimed polynucleotide sequence (SEQ ID NO: 23702) is sufficient for detecting any cancerous cell in any organism, assessing the tumor burden resulting from any cancer in any organism, and diagnosing any type of cancer in any organism (see pages 3-5), but only provides specific

information regarding the relationship between SEQ ID NO: 23702 and cancer in Working Example 105 (see pages 885-898). In this example, normal and cancerous tissues were collected from human subjects whose cancer status was already known, and RNA was isolated. cDNA probes were then prepared from this RNA and hybridized to arrays of probes (see pages 885-886). The resulting data are presented in Tables 159 and 160 (see pages 894-907).

Table 159 contains the results relevant to the claimed SEQ ID NO: 23702 (see page 897, columns 1-8 of the table). When cDNA from breast cancer patients was hybridized to the array, 17.39-26.09% of the patients showed an increased level of expression of SEQ ID NO: 23702. The number of breast cancer patients studied ranged from 18-23 individuals. In colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). In prostate cancer patients, 0.98 – 3.09% of the patients studied showed an increase in the expression level of SEQ ID NO: 23702. Here, the number of patients studied ranged from 64 individuals (1.56% showed increased expression) to 102 individuals (0.98 – 1.96% showed increased expression).

The specification does not teach in the working examples or elsewhere that the expression level of SEQ ID NO: 23702 is increased in any other types of cancerous cells, such as liver cancer, skin cancer, or lung cancer cells. The specification also does not teach detection of cancerous cells based solely on the expression of SEQ ID NO: 23702. In the above example, the disease status of the patients who contributed tissue to the study was already known (see page 885). Furthermore, the working example and specification only describes detection of cancerous cells in human subjects with one of three specific types of cancer, whereas the claims encompass

detection of any cancerous cell from any organism. Similarly, the specification does not teach diagnosing any type of cancer or assessing the tumor burden related to the presence of any cancer in any organism based solely on the expression level of SEQ ID NO: 23702. As discussed above, the working example only teaches measuring the expression level of SEQ ID NO: 23702 in human subjects with known disease status.

State of the Prior Art and Unpredictability

The art does not teach detecting cancerous cells, assessing tumor burden, or diagnosing cancer based on an observed increase in the expression level of SEQ ID NO: 23702. Regarding these methods, in general, however, the art teaches that it is entirely unpredictable whether or not the expression level of a particular gene can be used to detect cancerous cells, assess tumor burden, and diagnose cancer. For example, Russo et al. (Oncogene (2003) 22: 6497-6507) teaches that microarray-based gene expression studies are useful for rapidly assessing differential expression between cancerous and normal cells (see abstract and page 6497, column 2 – page 6498, column 1). However, Russo also teaches that different cancers showed differential expression of different genes (see pages 6498 – 6501, where Russo reviews the results of microarray-based expression profiling studies in prostate, oral, breast, and ovarian cancers), thereby demonstrating that the expression level of a single gene is unlikely to function in a diagnostic capacity for any type of cancer. Furthermore, Russo teaches that gene expression results can be unpredictable stating, "False microarray data can be generated from degraded mRNA (page 6503, column 2)." Russo also stated that unpredictability often results from the

fact that most human tissue samples used for expression analysis are a mixture of different cells (see page 6503, column 2).

The teachings of Srinivas et al. (The Lancet (2001) 2: 698-704) further support the conclusion that the claimed methods are highly unpredictable. Srinivas reviewed methods of cancer diagnosis and prognosis based on microsatellite instability, hypermethylation, single nucleotide polymorphisms, gene expression profiling, and proteomics (see abstract). Regarding the use of biomarkers such as differentially expressed genes for diagnostic purposes, Srinivas states, "The initial phase of biomarker discovery used to focus on single-marker-based approaches but, given the complexity of the carcinogenesis process, it would be difficult to correlate sufficiently any single biomarker to a specific cancer (page 699, column 1)."

The teachings of Reinholz et al. (Clinical Cancer Research (2005) 11(10): 3722-3732) provide further evidence of the level of unpredictability inherent in the claimed methods. Reinholz measured the ability of five markers, alone and in several different combinations, to accurately detect a specific type of cancer (breast cancer) in human subjects using RT-PCR to detect differential gene expression (see abstract). The resulting data show significant differences in specificity and sensitivity between the five markers (see Table 4 on page 3729), thus illustrating the unpredictable nature of reliably and reproducibly detecting even a single type of cancer in a human subject based on the observed expression level of a single gene. Reinholz specifically commented on the limitations of using a single marker for cancer detection stating, "Although *mammaglobin* is a promising tumor marker, it is not universally expressed in all breast cancers. Our results showed that ~20% of invasive breast cancer patients did not have detectable levels of *mammaglobin*. Therefore, we evaluated the utility of adding *B305D-C,*

B726P, GABA A_π, or *CK-19* to the analysis of *mammaglobin* to discriminate between patients with benign and invasive breast cancer breast biopsies. Our results showed that combining *mammaglobin* with *B305D-C* improved both sensitivity and specificity (page 3730, column 2)."

Finally, the disclosure of the instant application supports the conclusion that the claimed methods are highly unpredictable. As discussed above, Table 159 demonstrates that number of patients showing a statistically significant increase in expression of SEQ ID NO: 23702 varied widely between and within the cancer types tested. For example, in colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). Also, although the number of breast cancer patients showing increased expression levels of SEQ ID NO: 23702 did not show this extent of intra-cancer variation, the results differed markedly when compared to the colon and prostate cancer patients. These results clearly demonstrate the level of unpredictability present in the claimed methods.

Quantity of Experimentation

The quantity of experimentation required in this case is immense, because it would require significant study and experimentation including trials with hundreds of patients to determine that increased expression of the claimed polynucleotide is capable of reliably functioning to detect even one type of cancer in human subjects. Additional experimentation would also be required to demonstrate that over-expression of the claimed polynucleotide reliably functions as a reliable indicator of tumor burden related to the presence of a specific cancer in human subjects. Even further experimentation would be required to demonstrate that

an increase in the expression level of the claimed polynucleotide is an accurate and reliable diagnostic agent, capable of diagnosing a even a single type of cancer in human subjects. The amount of experimentation required in any of the above cases would be an inventive, unpredictable and difficult undertaking in itself, requiring years of inventive effort, with no guarantee of success at the conclusion.

The teachings in the pre- and post-filing art support this conclusion regarding the quantity of experimentation required to practice the claimed methods. For example, Feng et al. (Critical Reviews in Clinical Laboratory Sciences (2006) 43(5-6): 497-560) teaches that although discovery of promising biomarkers occurs with much less experimental effort than previously, validation of clinical utility remains slow and difficult (page 537, last paragraph). Feng stated, "Biomarker discovery may require only a few weeks and a small number of patient samples, whereas its validation may require thousands of samples from multi-center trials (page 537, last paragarph)." In addition, Feng teaches that detection of a differentially expressed gene does not always correlate with an increased level of protein product (page 538, paragraph), thereby illustrating that upon further experimentation, an initially promising biomarker may be eliminated as a useful diagnostic agent upon further testing. The teachings of Mitas et al. (International Journal of Cancer (2001) 93: 162-171) also illustrate the fact that validation of differentially expressed nucleic acids as useful diagnostic markers for even one type of cancer in human subjects requires extensive experimentation with no guarantee of success. Mitas analyzed the expression level of 12 cancer-associated genes by RT-PCR in tissue samples obtained from breast cancer patients (see abstract). Mitas reported that only half of the tested genes accurately functioned as breast cancer indicators in a specific type of breast cancer –

metastatic cancer (see abstract and page 166). As added evidence of the quantity of experimentation required for validating a single gene's predictive capabilities in even one cancer type, Mitas further taught that one of the tested genes, VEGF, although not of diagnostic utility for metastatic breast cancer, could be useful in detecting primary breast cancer (page 169, column 1). Thus, Mitas teaches the same marker may not function as an accurate diagnostic agent for all cancers and further that initially promising genes may not prove to be useful markers upon further analysis. Finally, Srinivas summarizes the extensive effort required to establish the diagnostic value of even a single biomarker in a single cancer in human subject. Srinivas states at pages 702-703:

> The sensitivity, specificity, and predictive value of biomarkers have to be determined through use of body fluids, paired tumours, and surrounding tissue from a wide variety of cancers before they can be used in populations. Many samples from individuals with known characteristics should be processed, to minimize the problems of confounding and to avoid spurious associations. Before field-testing, it should be established that the biomarker is truly in the path of pathogenesis and not merely the result of an adaptive response. Case-control studies on stored samples should be used to test the efficiency of the biomarkers. Although the emerging technologies show great promise, care must be taken to define and establish references or baseline profiles from normal tissue, cells, or body fluids. Extensive animal studies may help refine human testing before screening. The biomarker assay should be reproducible to avoid false-positive and false-negative results and also to provide a substantial lead-time before clinical diagnosis.

Based on these teachings of Feng, Mitas, and Srinivas, it must be concluded that the quantity of experimentation required is very large.

The Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the instant claims are broadly drawn to methods of detecting any type of cancerous cell in any organism, assessing the tumor burden resulting from any cancer in any organism, and diagnosing any cancer in any organism based solely on an observed increase in the expression level of SEQ ID NO: 23702. Despite the breadth of the claims, the specification only teaches detection of cancerous cells from human subjects known to have one of three types of cancer, and even these limited results show a high degree of variability (i.e. unpredictability). Furthermore, the specification provides no guidance regarding methods of validation or how to overcome the art-recognized problems of reliable diagnosis based on the expression level of a single gene. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

No claims are currently allowable.

This Office action has an attached requirement for information under 37 CFR 1.105. A complete reply to this Office action must include a complete reply to the attached requirement for information. The time period for reply to the attached requirement coincides with the time period for reply to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
April 12, 2007

amb

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600